Determining the potential sites of neural adaptation to cross-education: Implications for the cross-education of muscle strength.

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Abstract

Cross-education describes the strength gain in the opposite, untrained limb following a unilateral strength training program. Since its discovery in 1894, several studies now confirm the existence of cross-education in contexts that involve voluntary dynamic contractions, eccentric contraction, electrical stimulation, whole-body vibration and, more recently, following mirror feedback training. Although many aspects of cross-education have been established, the mediating neural mechanisms remain unclear. Overall, the findings of this review show that the neural adaptations to cross-education of muscle strength most likely represent a continuum of change within the central nervous system that involves both structural and functional changes within cortical motor and non-motor regions. Such changes are likely to be the result of more subtle changes along the entire neuroaxis which include, increased corticospinal excitability, reduced cortical inhibition, reduced interhemispheric inhibition, changes in voluntary activation and new regions of cortical activation. However, there is a need to widen the breadth of research by employing several neurophysiological techniques (together) to better understand the potential mechanisms mediating cross-education. This fundamental step is required in order to better prescribe targeted and effective guidelines for the clinical practice of cross-education. There is a need to determine whether similar cortical responses also occur in clinical populations where, perhaps, the benefits of cross-education could be best observed.

Key words: Connectivity, Cross-education, Mirror neurons, Excitability, Inhibition, Twitch force.

List of Abbreviations

1-RM: one-repetition maximum

BOLD: blood oxygenation level dependant

FCR: flexor carpi radialis

fMRI: functional magnetic resonance imaging

FDI: First Dorsal Interosseous

GABA: γ-Aminobutyric acid

IHI: interhemispheric inhibition

LICI: long-interval intracortical inhibition

MEPs: motor-evoked potentials

MNS: mirror neuron system

MRI: magnetic resonance imaging

MVC: maximal voluntary isometric contraction

M1: primary motor cortex

rTMS: repetitive transcranial magnetic stimulation

sEMG: surface electromyography

SICI: short intracortical inhibition

tDCS: transcranial direct current stimulation

TMS: transcranial magnetic stimulation

VA_{TMS}: voluntary activation measured with TMS

WBV: whole-body vibration training

Introduction

There is compelling evidence to support the hypothesis that a change in habitual physical activity, such as strength training, can induce adaptations in the nervous system (Duchateau et al. 2006; Gabriel et al. 2006; Carroll et al. 2011). One common observation that underscores the complexities of neural adaptations following a period of strength training is cross-education. This phenomenon specifically refers to the increase in muscle strength in one limb following unilateral strength training of the opposite limb (Manca et al. 2017a). Since the original observation by Scripture et al. (1894), there are now many published reports that have confirmed that the cross-education of muscle strength is a real effect (Manca et al. 2017a); however, the neural mechanisms mediating cross-education are less clear (Ruddy and Carson 2013). Over the last 30 years, several studies have used surface electromyography (sEMG) recordings (Cannon and Cafarelli 1987, 1992; Mason et al. 2017a), electrical stimulation of peripheral nerves (Dragert and Zehr 2011; Fimland et al. 2009; Lagerquist et al. 2006), transcranial magnetic stimulation (TMS) (Goodwill et al. 2012; Hortobágyi et al. 2011; Manca et al. 2016a; Mason et al. 2017a), voluntary activation measured with TMS (VA_{TMS}) (Lee et al. 2009) and functional magnetic resonance imaging (fMRI) (Farthing et al. 2007; Palmer et al. 2013; Ruddy et al. 2017) to study the neural adaptations to cross-education. Unfortunately, the neural mechanisms associated with cross-education remain elusive. Reports in the literature are markedly different and range from no substantial change (Latella et al. 2012) to persistent bilateral increases in corticospinal excitability (Hendy et al. 2015), reductions in corticospinal inhibition (Coombs et al. 2016), and short-interval intracortical inhibition (Hortobágyi et al 2011). The complexity is further magnified because emerging evidence suggests some structural changes occur in both motor and non-motor areas (Ruddy et al. 2017). Furthermore, recent work has suggested that other brain regions and systems, such as the mirror neuron system (MNS) (Zult et al. 2016) and functional and structural connectivity (Ruddy et al. 2017)

could be important neural adaptations to cross-education. Subsequently, the aim of this narrative review is to critically evaluate and elucidate some of the reported important neural mechanisms and adaptations that have been implicated in the cross-education of muscle strength, and the potential implications of this phenomenon to clinical populations. This will be achieved by exploring the idea that the neural adaptations to cross-education are due to structural and functional changes within cortical motor and non-motor regions and subtle changes along the entire neuroaxis. This will be addressed by critically appraising the literature where neuroimaging and electrophysiological techniques, such as fMRI, TMS, VA_{TMS} and spinal cord reflex studies have been used to explore the potential sites of neural adaptations to cross-education. Secondly, interventions which have been utilised to enhance the cross-education effect are then considered including, the mirror neuron system, non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS), electromyostimulation and vibration training. Lastly, the potential clinical implications of cross-education are considered.

Evidence for cross-education of muscular strength

Since the first documentation of cross-education (Scripture et al. 1894), there has been a widespread fascination among the scientific community about the phenomenon whereby strength training of one limb results in an increase in strength of the opposite, untrained limb (Carroll et al. 2006; Munn et al. 2004). This phenomenon has been summarised in a recent meta-analysis by Manca et al. (2017a) that revealed a pooled cross-education effect on muscle strength of 11.9%. Following a quantitative analysis of 31 studies which drew data from 785 subjects, the authors found a 9.4% effect for the upper limb and 16.4% for the lower limb (see Table 1A-D). The pooled contralateral increase in strength was substantially greater than originally reported (a pooled 7.8% increase (3.8% for the upper limb and 10.4% for the lower limb) from 16 studies involving 449 subjects (Carroll et al. 2006)). Of particular interest,

Manca et al. (2017a) demonstrated that the cross-education effect was not restricted to a particular contraction type, but is applicable to the entire muscle action spectrum across both upper and lower limbs. Although the magnitude of cross-education does differ between contraction type (isometric 8.2%; concentric 11.3%; eccentric 17.7%; isotonic-dynamic training 15.9%), all modes significantly increase contralateral strength following unilateral strength training (Manca et al. 2017a). Based upon these findings, it is likely that cross-education could be applied in context-specific environments, such as during different phases of musculoskeletal rehabilitation, in an attempt to maximize the cross-education of muscular strength and to attenuate strength loss and muscle atrophy following injury.

Upper and lower limb effects

The net effect of unilateral strength training of the upper limb is a contralateral increase in strength of 9.4% (Manca et al. 2017a). Of the 13 studies (two studies were excluded due to high heterogeneity) included by Manca et al. (2017a), five studies examined the hand/wrist muscles (Cannon and Cafarelli 1987; Coombs et al. 2016; Farthing et al. 2005; Manca et al. 2016a; Yue and Cole 1992), two examined the wrist muscles (Kidgell et al. 2015; Lee et al. 2009b) and six examined the elbow flexor muscles (Farthing and Chilibeck 2003; Kidgell et al. 2011; Meyers 1966; Munn et al. 2005; Shaver 1970, 1975). Although the cross-education model evidently exists in the upper limb, it appears that the effect is greater for the lower-limb musculature with a 16.4% increase in contralateral strength reported (15 studies [one study excluded due to high heterogeneity]) (Manca et al. 2017a). Most of the studies that were included in this recent meta-analysis involved training the knee extensors (12 studies) (Abazović et al. 2015; Carolan and Cafarelli 1992; Coratella et al. 2015; Garfinkel and Cafarelli 1992; Goodwill et al. 2012; Hortobágyi et al. 1996, Hortobágyi et al. 1999; Kannus et al. 1992;

Latella et al. 2012; Lepley and Palmieri-Smith 2014; Weir et al. 1995, Weir et al. 1997), whilst the remaining studies examined the ankle muscles (four studies) (Fimland et al. 2009; Lagerquist et al. 2006; Manca et al. 2015; Shima et al. 2002). Interestingly, the magnitude of strength transfer was considerably more variable in the upper limb with a heterogeneity of 26% compared to the lower limb of 9% (Manca et al. 2017a). Although both heterogeneity scores are on the lower end of the continuum, it appears that the responses following strength training of the lower limb are uniform across different muscles and contraction modes. This difference may reside in the capacity to voluntarily activate the muscle of the upper or lower limb. The level of neural drive (i.e., motor output) to a muscle, which is also known as 'voluntary activation', can be assessed with the twitch interpolation technique (Allen et al. 1998) and via TMS cortical voluntary activation (e.g., VA_{TMS}) (Carroll et al. 2008). Incomplete voluntary activation is associated with a reduction in the 'voluntary' force generating capacity of the muscle due to reduced neural drive at or above the site of stimulation of the motor nerve. It has been suggested that the capacity to increase muscle strength in upper-limb muscles may be limited when compared to lower-limb muscles due to high pre-existing levels of voluntary activation (Lee et al. 2009a) when compared to the lower-limb muscles (Ross et al. 2007; Sidhu et al. 2009). However, at present, there are not enough high-quality studies that have measured voluntary activation to conclude any differences, despite the recent finding, for at least the trained-limb voluntary activation is improved in the upper limb following strength training (Nuzzo et al. 2017). Although the magnitude of cross-education appears to be different between the upper and lower-limb muscles, other factors, such as contraction type (i.e., isometric, concentric, eccentric and isotonic) and the novelty of the training task are likely to influence the magnitude of cross-education (Farthing et al. 2005; Manca et al. 2017a).

Contraction type

169 At present, the greater part of cross-education studies has focused on the use of
170 isometric and concentric training (Carroll et al. 2006; Manca et al. 2017a; Munn et al. 2004).
171 However, eccentric contractions are known to provide a powerful stimulus for strength
172 increases in the exercised and non-exercised limbs (Hortobágyi et al. 1997). This is supported
173 by the finding of Manca et al. (2017a) who reported that eccentric and dynamic training
174 protocols (i.e., concentric and eccentric contractions) induced significantly greater contralateral
175 gains in strength than isometric contractions (eccentric 17.7%, dynamic 15.9% vs isometric
176 8.2%). However, the number of studies using eccentric and dynamic training protocols is
177 considerably less than those using isometric and concentric training protocols (Manca et al.
178 2017a). Irrespective of this, the available evidence clearly indicates that the contralateral
179 increase in muscle strength is real. This effect is strongest when the training employed has been
180 matched to the strength outcome, showing that training specificity is very important (Kidgell
181 et al. 2015; Manca et al. 2017a).

182 In the clinical context, it would be desirable to utilise a cross-education model that is likely
183 to impart the greatest amount of strength transfer, thus training and testing specificity must be
184 considered. Because the cross-education literature suggests that the magnitude of transfer is
185 contraction-mode specific, the true benefits of cross-education will depend on how effective
186 this contraction-mode training is within clinical populations. For example, it would be
187 beneficial to explore whether eccentric training also transfers the largest amount of strength in
188 different clinical populations. Furthermore, understanding the clinical effects of cross-
189 education is important because the ability to activate muscles and produce force is critical for
190 a number of activities of daily living. For example, there is a good correlation that exists
191 between muscle strength and several clinical outcomes such as, gait speed (Suzuki et al. 2002),
192 decreased risk of falls (Spink et al. 2011), and better balance (Moreland et al. 2004); also,
193 people with greater strength levels tend to live longer (Legrand et al. 2014). In this regard,

understanding the neurophysiological changes that occur in the corticospinal tract and within motor and non-motor regions following a cross-education intervention is important, as it will advance our understanding of the neural adaptations that accompany the cross-education of muscle strength.

Importance of the corticospinal tract as a potential site for neural adaptation to cross-education

The spinal cord is under the control of a number of neurones that descend from the primary motor cortex (M1). The largest of these are the corticospinal neurones that have their origins in layer V of the cerebral cortex and extend to form the bulk of the corticospinal or pyramidal tract (Porter, 1985). Although corticospinal neurones are located within six cortical regions, the M1 has the largest concentration (Porter, 1985). Within the M1, these corticospinal neurones are functionally organised to project to motoneurones that control specific muscle groups (Porter, 1985; He et al. 1993). Corticospinal neurones that arise within the M1 descend through the internal capsule, brainstem, and medulla oblongata to continue to descend in the dorsolateral funiculi of the spinal cord (Alawieh et al. 2017).

As the corticospinal neurones leave the M1 and descend to the medulla, they are organised somatotopically. At the medullary spinal junction, approximately 85-90% of the corticospinal neurones cross the midline to form the motor pyramidal decussation (Alawieh et al. 2017), where they continue as the dorsolateral funiculi of the spinal cord and converge onto motoneurones within the ventral horn of the spinal cord that innervate limb muscles (Alawieh et al. 2017). Anatomical mapping studies reveal that the connectivity of the corticospinal tract suggests that the remaining uncrossed ipsilateral corticospinal tract fibres descend primarily in the dorsolateral lateral or ventral funiculi of the spinal cord (Alawieh et al. 2017).

The ipsilateral corticospinal tract projections could have important implications for the cross-education of muscle strength as there is emerging evidence that suggests a potential site for adaptation could reside within the ipsilateral M1 itself (Goodwill et al. 2012; Kidgell et al. 2011; Lee et al. 2010; Mason et al. 2017a). A small proportion of corticospinal tract fibres do not crossover at the pyramidal decussation at the medulla; rather, they project to ipsilateral spinal motoneurons, where they could alter the excitability of ipsilateral pathways (Alawieh et al. 2017; Carson, 2005). In the clinical neurophysiology literature, it has been suggested that increased utilisation of the ipsilateral pathway may provide a viable method for re-establishing motor control of upper-limb muscles following lesions to the M1 (Alawieh et al. 2017).

Techniques to investigate the functional properties of the brain

The ability to examine the human central nervous system (CNS) has developed remarkably over the last 30 years. Imaging techniques such as fMRI and positron emission topography (PET) indirectly measure the changes in blood flow associated with neural activity while participants perform a particular motor task (Jenkins et al. 1994). For example, there is a relationship between isometric force production, pre-movement activity and actual movement execution that results in increased cortical activity in the M1, supplementary motor area (SMA) and the dorsal portion of the anterior cingulate cortex (Dettmers et al. 1995; Thickbroom et al. 1999; Farthing et al. 2007). Recently, neuroimaging techniques have been used to provide insight into the potential neural adaptations to cross-education (Farthing et al. 2007, Palmer et al. 2013; Ruddy et al. 2017). Although these studies demonstrate changes in blood flow during movement preparation and execution, they do not provide any objective data concerning the excitatory and inhibitory synaptic events specific to the M1 during movement (Hallett 2007). TMS, a non-invasive neurostimulatory technique, can provide a solution to

some of these limitations as it allows the net excitatory and inhibitory synaptic activity within the M1 and corticospinal tract to be determined with excellent time resolution (Hallett 2007). There is now a growing body of evidence that shows that there are changes in the efficacy of neural transmission along the corticospinal tract following cross-education (Goodwill et al. 2012; Kidgell et al. 2011; Lee et al. 2009; Mason et al. 2017a) and new regions of activation as assessed by fMRI (Farthing et al. 2007; Palmer et al. 2013; Ruddy et al. 2017).

Structural and functional cortical activity and cross-education

The cross-education of muscle strength has historically been associated with changes in the neural control of the untrained limb, namely, increased capacity to voluntarily activate the untrained muscle. This observation is based upon the change in strength of an untrained limb which occurs in the absence of muscle hypertrophy, although changes in the intrinsic properties of the untrained homologous muscle cannot be excluded (Hendy and Lamon 2017). Despite possible muscle effects, the consensus suggests that the cross-education effect, in part, is mediated by changes in the activity of neural circuits, but the site of such change (i.e., cortical or subcortical) remains unclear. It is not known whether bilateral corticospinal excitability and inhibition generated during unilateral motor training are the genesis for concurrent neural adaptations in both cerebral hemispheres (Hellebrandt 1951). Although studies have reported bilateral activation of the M1 during unilateral movements (Kobayashi et al. 2003; Ruddy et al. 2016), to date, there are few studies that have reported bilateral cortical activity of the M1 following cross-education of muscle strength (Frazer et al. 2017; Hendy and Kidgell 2014; Hendy et al. 2015; Mason et al. 2017a). An emerging approach that may add new knowledge regarding the neural adaptations underpinning the cross-education is the use of neuroimaging techniques. There are now several neuroimaging studies that show, that during unilateral

movements, several regions of activation within pre-motor areas outside of the M1 are involved. These recent findings suggest that there is a greater need to understand the structural and functional bases of cross-education (Farthing et al. 2007; Koeneke et al. 2004) and their causal effect in increasing muscle strength of the untrained limb.

Neuro-imaging and cross-education

Evidence suggests that the cerebral responses to cross-education are controlled centrally by communication between the cerebral hemispheres, via interhemispheric communication and bilateral cortical activity (Hortobágyi et al. 2011; Perez and Cohen 2009). There is a growing need to obtain detailed knowledge of the structural and functional connectivity patterns within the brain following cross-education training. In vivo neuroimaging, such as spatiotemporally resolved magnetic resonance imaging (MRI), alongside its functional variant, fMRI, is one of the pre-eminent tools that is capable of capturing the interaction between neural substrates and action in humans. fMRI is a non-invasive technique that detects changes in regional blood flow within cortical structures in response to a motor task and is quantified as a change in the blood oxygenation level dependant (BOLD) contrast or ratio of deoxygenated haemoglobin (Kelly and Garavan 2005). Changes in the BOLD response are representative of a change in the activation of neural circuits (Xiong et al. 2009), but the BOLD response is not a direct mesaure of synaptic activity or the presence action potential acitivity. Thus, any interpretation from BOLD changes should be made with caution as a number of biological process may be involved. For example, changes in activation could be accompanied by changes in synaptic activity within brain structures that are involved in movement (Palmer et al. 2013). Nevertheless, fMRI has been used to detect temporal correlations in spontaneous BOLD responses while subjects remain at rest. These BOLD responses reveal that multiple cortical brain regions are

functionally connected forming resting-state networks. Interestingly, the level of functional connectivity within resting-state networks suggests the existence of direct structural (i.e., neuroanatomical) connections between functionally-linked brain regions (Cordes et al. 2001). Such structural and functional connectivity facilitates the ongoing inter-regional neuronal communication. Importantly, the structural integrity of white-matter tracts, which are structural neural pathways within the brain, facilitates the transmission of neural communication from one brain region to another (Greicius et al. 2009). Understanding changes in structural and functional connectivity following cross-education will add new knowledge regarding the potential sites and mechanism of strength development for the untrained limb.

Regions of cortical activation and their implications for cross-education

There is experimental evidence that suggests regions outside, but functionally connected to the M1, may mediate the neural adaptations of cross-education (Farthing et al. 2007; Ruddy et al. 2017; see Table 1). For example, during unilateral movements, there are larger increases in the BOLD response within the premotor cortex (Koeneke et al. 2004), supplementary motor area (Grafton et al. 2002) and cingulate motor area (Kermadi 2000). Structural connectivity reveals that the dorsal premotor cortex, supplementary motor area and cingulate motor area have dense structural white-matter connections within the homologous zone in the opposite cerebral hemisphere (Ruddy et al. 2017). At a minimum, this suggests that a structural basis exists for cross-education and may be a specific neural strategy used by the nervous system for increasing the strength of an untrained limb. This line of inquiry is supported when assessing the functional importance of these structural connections. The supplementary motor area is a critical region for motor learning as it plays an important role in modulating the timing of force output (Haller et al. 2009) and is associated with cortical plasticity following motor learning (Grafton et al. 1995, 2002; Perez et al. 2007b). In addition, the supplementary motor area controls both the contralateral and ipsilateral limbs during

sequence motor learning (Brinkman and Kuypers 1973). Perez et al. (2007b) showed that when repetitive TMS (rTMS) was applied to the supplementary motor area, it abolished the cross-transfer of a sequenced motor-learning task to an untrained limb, but it had no effect on the performance gains of the trained limb. Recent evidence now confirms that the structural connectivity of bilateral supplementary motor areas is substantially greater than any other bilateral regions of the motor cortical network (e.g., M1; Ruddy et al. 2017). In support of this, Ruddy et al. (2017) showed that, following an acute bout of 300 ballistic wrist-flexion movements, motor performance of the untrained limb improved and was associated with an increase in functional connectivity between the right and left supplementary motor area. These observations show that unilateral motor-training engages interhemispheric pathways and that the level of structural connectivity (i.e., the connecting white-matter pathways) influences the magnitude of cross-education (Ruddy et al. 2017). Although this provides new evidence and a good rationale for other cortical structures to be involved in the cross-education of muscle strength, to date, there have been no long-term cross-education studies to show that there are persistent changes in connectivity between left and right supplementary motor areas.

The dorsal premotor region has strong bilateral connections to the prefrontal cortex, parietal cortex and striatum, and this may also serve as a pathway mediating cross-education of strength. In primates, stimulation of the premotor cortex leads to an observable twitch response, showing its contribution to motor output during movement (Dum and Strick 2005; He et al. 1995). Further, because the dorsal premotor cortex has direct projections to the spinal motoneurone pool and shared connections with the ipsilateral M1, it is a candidate structure that could modulate the output from the M1 following cross-education (He et al. 1993). Neuroimaging data support strong interhemispheric bilateral connections between the dorsal premotor cortices (Fling et al. 2011), and structural connectivity reveals that the anterior dorsal premotor area has connections to the prefrontal cortex, whilst the posterior regions have direct

projections to the M1 and spinal cord (Schubotz and von Cramon 2002). These structural and functional connections provide cortical loci that could mediate cross-education. However, a caveat to this interpretation is that there have been no cross-education studies that have examined the pattern of activation within the dorsal premotor cortex. Rather, most of the current understanding for this region is based upon the motor-learning literature (Hardwick et al. 2013). A significant drawback with imaging is that changes in the fMRI BOLD signal do not reveal any changes in the synaptic behaviour regarding these new regions of cortical connetivity.

A cortical network, not thoroughly explored, that could contribute to cross-education is the cingulate motor area. The cingulate motor area is active during unilateral limb movements but, importantly, the level of activation increases as a function of increased force output (Winterer et al. 2002). It is likely that chronic high-force unilateral training may result in persistent changes in connectivity of the cingulate motor area. This hypothesis is possible because of the strong connections between the cingulate motor area and the homologous region in the opposite cerebral hemisphere (Ruddy et al. 2017).

Neuroimaging studies and cross-education

The origins of structural and functional connectivity provide the opportunity to explore brain networks following cross-education; however, to date, there has only been one acute cross-education study (i.e., a single training bout) (Ruddy et al. 2017) and two long-term cross-education studies (six and four week training interventions) (Farthing et al. 2007; Palmer et al. 2013) that have used neuroimaging to determine potential sites and patterns of cortical activation.

Using a ballistic training task for the left-wrist flexors, Ruddy et al. (2017) demonstrated that the increase in performance of the untrained limb was 83% of that observed for the trained limb, and that there was a significant increase in functional connectivity in the resting motor network between the right and left supplementary motor areas. Interestingly, the increase in functional connectivity was not associated with the individual level of cross-education. Intriguingly, fibre density in the neural tracts (white matter) connecting the bilateral supplementary motor areas was negatively correlated with cross-education. Although this was only an observation following an acute bout of unilateral motor training, the finding suggests that interhemispheric pathways and the structural integrity of the connecting white-matter pathways of the supplementary motor area play a crucial role in cross-education. Although this is an interesting finding, it remains unclear if repeated high-force voluntary contractions performed over 2-4 weeks lead to a similar effect in structural and functional connectivity.

Farthing et al. (2007) were the first to examine the training-related effects of cross-education on patterns of brain activation following a six-week unilateral strength-training intervention. Strength of the left untrained limb improved by 47% and there was a persistent increase in activation of the sensorimotor cortex and bilateral M1, which is consistent with the motor-learning literature (Grafton et al. 2002). The cross-education of strength was also accompanied by an increase in the pattern of activation within the temporal lobe and the right and left cerebellum (Farthing et al. 2007). Because there was an increase in activation of the M1, supplementary motor area and temporal region following cross-education, this finding supports the recent evidence from Ruddy et al. (2017) that there are structural and functional changes within cortical networks following unilateral motor practice.

Palmer et al. (2013) examined the effects of four-weeks of strength training of the lower limb on structural connectivity. Training consisted of six sets of six maximal voluntary contractions (MVCs) of the dominant-leg plantar flexors. MVC was measured pre and post for

389 the trained and untrained leg. Strength training increased plantar flexion strength by 30% in
390 the untrained limb; however, this change was not accompanied by any structural brain changes
391 which is in contrast to the findings of Farthing et al. (2007). Physiological interpretation of
392 changes in regions of brain activation obtained from fMRI should be made with caution as
393 there could be a range of other physiological processes that supplement changes in brain
394 activation, such as neuronal activation from between and within brain regions that occur during
395 movement. Therefore, there is a need to examine the muscle-specific pattern of cortical activity
396 following upper- and lower-limb cross-education using multiple techniques.

397 In light of the above, given the recent emergence of neuroimaging data, it seems
398 reasonable to suggest that the cross-education of strength is associated with patterns of brain
399 activation because of repeated training. The finding of increased activation of the temporal
400 region following cross-education has important implications for understanding the mechanisms
401 of strength transfer (Farthing et al. 2007). For some time, cross-education has been considered
402 a form of motor learning and there are several lines of evidence that the temporal region is
403 important for memory recall (Martin et al. 1995). In theory, memory retrieval could be
404 important for cross-education in regards to providing an internal representation of a movement
405 previously acquired by the opposite limb (Obayashi 2004). This hypothesis supports earlier
406 findings within the motor-learning literature where the temporal region has been implicated
407 (Farthing et al. 2007). Increased activation within the right and left cerebellum also suggests
408 that cross-education training may improve the timing and activation of agonists, antagonists
409 and synergist muscle groups which improve the coordination of a movement task. There is
410 good evidence that cross-education training improves patterns of muscle activation (Cannon
411 and Cafarelli 1987; Carolan and Cafarelli 1992; Farthing et al. 2005; Fimland et al. 2009;
412 Garfinkel and Cafarelli 1992; Mason et al. 2017a; Perez et al. 2007a) and such changes are
413 likely a result of changes in activation of the cerebellum (Obayashi 2004).

Although new regions of activation have emerged as potential sites of adaptation following cross-education, fMRI is not able to determine the intracortical mechanisms underlying increased activation. For example, it remains unclear whether excitatory or inhibitory mechanisms underlie the changes in the BOLD responses (Logothetis 2003). Therefore, there is a need to combine neuroimaging techniques with electrophysiological techniques, such as single- and paired-pulse TMS and quantitative electroencephalography, to determine the spatial and temporal effects of cross-education.

Neurophysiological mechanisms mediating cross-education

A consistently reported neural adaptation to cross-education is bilateral cortical activity (Frazer et al. 2017; Hendy and Kidgell 2014; Lee et al. 2010) whereby, during unilateral strength training, there is concurrent activation in both cerebral hemispheres that are involved in motor output. The M1 ipsilateral to the training limb has been shown to play an important role in mediating the cross-education effect (Frazer et al. 2017; Hendy et al. 2015; Hortobágyi et al. 2011; Lee et al. 2010). Specifically, cross-education studies have reported increased corticospinal excitability (Kidgell et al. 2015), decreased corticospinal inhibition (Coombs et al. 2016; Hendy et al. 2015), reduced interhemispheric inhibition (IHI) (Hortobágyi et al. 2011; Zult et al. 2016) and increased VA_{TMS} (Lee et al. 2009b) in the M1 ipsilateral to the training limb.

The use of TMS to examine the cortical responses to cross-education

TMS is one of the most robust tools available to study the function of the M1 following a motor-training intervention. Briefly, TMS requires placing a wire coil over the M1 ‘hot spot’ of the target representation of the trained muscle (Hallett 2007). When the magnetic coil is

438 discharged over the M1, it generates a brief (≤100 μs) high-current pulse that passes painlessly
439 through the skull (Hallett 2007; Rothwell et al. 2009). When the intensity of the TMS pulse is
440 sufficiently large, it primarily activates cortico-cortical axons which provide excitatory inputs
441 onto corticospinal output neurones, depolarising them trans-synaptically as I-waves, with some
442 in close proximity to the axon hillock as D-waves (Di Lazzaro et al. 1999). The net result is the
443 production of a series of descending volleys (action potentials) that travel along the
444 corticospinal tract, synapsing at the appropriate lower-motoneurone pool within the spinal cord,
445 eliciting a brief, relatively synchronous muscle response in the contralateral side of the body.
446 The response is recorded using sEMG and is referred to as a motor-evoked potential (MEP)
447 (Hallett 2007).

448 MEPs represent the balance between the net excitatory and inhibitory influences on the
449 corticospinal tract as a whole, including those from cortical circuitry, the motoneurone pool,
450 and spinal interneuronal relays (Hallett 2007; Kidgell et al. 2017). Therefore, it is difficult to
451 ascertain the exact site(s) of adaptation with a single-pulse TMS protocol following a motor-
452 training intervention; however, MEPs still provide several important physiological variables
453 that represent the overall efficacy of neural transmission along the corticospinal tract (Rossini
454 and Rossi 2007). The amplitude of the MEP reflects the integrity of the corticospinal tract, the
455 excitability of the M1, and the efficiency of neural conduction along the peripheral motor
456 pathway (Hallett 2007). Conversely, the corticospinal silent period, a period of electrical
457 silence immediately following a MEP evoked in an active muscle, represents inhibition along
458 the corticospinal tract (Wilson et al. 1993). The early portion (50-75 ms) is primarily caused
459 by segmental mechanisms, such as Renshaw cell recurrent inhibition and activation of Iα
460 interneurones by descending corticospinal volleys. The latter portion (>75 ms) is caused by
461 cortical gamma-aminobutyric acid (GABA), specifically $GABA_B$ contributions (Fuhr et al.
462 1991). There are now several cross-education studies that have examined the MEP amplitude

and corticospinal silent period duration of the M1 ipsilateral to the trained limb (Coombs et al. 2016; Goodwill et al. 2012; Hortobágyi et al. 2011; Kidgell et al. 2011, 2015; Latella et al. 2012; Manca et al. 2016a; Mason et al. 2017a). However, the findings are mixed. For example, some studies have reported increased MEP amplitudes (Mason et al. 2017a; Hendy et al. 2015), whilst others have shown no change (Coombs et al. 2016; Latella et al. 2012); those that examined the corticospinal silent period have shown reductions (Coombs et al. 2016, Kidgell et al. 2015).

Although single-pulse TMS can provide useful information about the excitability of the corticospinal tract, paired-pulse TMS allows an objective assessment of the physiology of the intrinsic cortico-cortical connections within the M1 (Kujirai et al. 1993). Paired-pulse TMS that uses a sub-threshold conditioning stimulus (70-80% motor threshold), delivered 2-4 ms prior to a supra-threshold test-stimulus, results in a suppressed paired-pulse MEP compared to a baseline single-pulse MEP (Rothwell et al. 2009). This protocol allows the estimation of the excitability of $GABA_A$-ergic circuits within the M1 by calculating the ratio between the conditioned and unconditioned MEPs, which is known as short-interval intracortical inhibition (SICI). SICI is synaptic in origin and mediated by the activation of low-threshold inhibitory circuits that have a presence of $GABA_A$ receptors from the sub-threshold conditioning stimulus (Kujirai et al. 1993). Paired-pulse TMS enables the measurement of synaptic efficacy of inhibitory neural networks detectable at the level of the M1 following cross-education (Goodwill et al. 2012). In fact, several cross-education studies have now shown that SICI is reduced within the M1 ipsilateral to the training limb (Goodwill et al. 2012; Kidgell et al. 2015).

In a similar manner, when a suprathreshold TMS pulse at an inter-stimulus interval (ISIs) of 50-200 ms is applied, MEPs are significantly reduced and are referred to as long-interval intracortical inhibition (LICI) and this is representative of a slow-phase inhibitory circuit (Valls-Solé et al. 1992). Similar to the corticospinal silent period, LICI is thought to

488 reflect $GABA_B$-mediated cortical inhibition. To date, there has only been one study that has
489 examined the effect of cross-education on LICI and it reported no changes in LICI in the
490 ipsilateral M1 (Manca et al. 2016a).

491 Although TMS is an emerging technique that can be used to provide insight into the
492 neural adaptations to cross-education, there are several limitations that should be considered
493 when interpreting the literature. It must be recognised that the amplitude of MEPs are
494 influenced by numerous factors along the brain-to-muscle pathway. For example, the
495 excitability of the corticospinal and intracortical neurones that are activated by TMS and the
496 efficacy of the synapses between these neurones can influence MEP amplitude (Mazzocchio et
497 al. 1994; Ugawa et al. 1995). Further, the excitability of interneurones located between
498 corticospinal neurones and α-motoneurones, the efficacy of the corticospinal-motoneuronal
499 synapses (Bunday and Perez, 2012; Taylor and Martin, 2009), and the excitability of the
500 motoneurones themselves (Nielsen and Petersen, 1995; Di Lazzaro et al. 1998), all affect the
501 amplitude of MEPs.

502 ***Ipsilateral MEP responses to cross-education***

503 There are now several studies that have reported that cross-education of muscle strength
504 is accompanied by an increase in ipsilateral corticospinal excitability (i.e., MEPs) following
505 dynamic, eccentric and concentric training, (Goodwill et al. 2012; Kidgell et al. 2011; Mason
506 et al. 2017a), eccentric (Kidgell et al. 2015) and isometric strength-training (Hortobágyi et al.
507 2011). However, similar to the TMS strength-training literature, this finding is not always
508 consistent (Kidgell et al. 2017). For example, just as many studies have shown no change in
509 ipsilateral corticospinal excitability (Coombs et al. 2016; Latella et al. 2012; Manca et al.
510 2016a). These inconsistencies appear to be driven by the different TMS methods employed,

511 muscles trained, intensity of the training stimulus, and the mode of muscle contraction used
512 during training.

513 Historically, the cross-education effect was thought to be confined to the contralateral
514 homologous muscle; however, recent experimental data suggested that the effects exist beyond
515 the contralateral agonist muscle (Mason et al. 2017a). Recently, we (Mason et al. 2017a)
516 examined the spatial effects of cross-education on ipsilateral corticospinal excitability. Briefly,
517 participants completed 3-weeks of high intensity (80% one repetition maximum [1-RM])
518 elbow-flexion training and we recorded MEPs from agonist and synergist muscles by
519 stimulating ipsilateral M1 prior to, and following, the training period. The MEPs of the
520 untrained elbow-flexors increased but there were no changes in MEPs of the untrained
521 synergistic wrist-flexors (Mason et al. 2017a), yet we showed increased strength in both the
522 contralateral agonist and synergist. We also reported a similar finding for corticospinal silent
523 period duration. These findings raise questions as to why there was not any increase in the MEP
524 and any decrease in corticospinal silent period duration of the synergist muscle despite
525 reporting an increase in strength. As alluded to earlier, it is likely the spatial effects of strength
526 transfer could be mediated by other cortical structures, but functionally linked to the ipsilateral
527 M1 that TMS is unable to detect. Overall, the ipsilateral MEP responses to cross-education are
528 inconsistent across studies and confined to the contralateral homologous motor-cortical
529 network. To this end, there is no clear evidence to support a role for increased corticospinal
530 excitability of the M1 ipsilateral to the training limb as a mechanism that mediates the cross-
531 education of strength (see Table 2).

532 ***Ipsilateral inhibitory responses to cross-education***

533 Unlike the MEP responses to cross-education, there is stronger evidence that shows an
534 important neural adaptation to cross-education is a reduction in intracortical inhibition of the

535 ipsilateral M1 (Coombs et al. 2016; Goodwill et al. 2012; Hortobágyi et al. 2011; Kidgell et al.
536 2015; Latella et al. 2012; Mason et al. 2017a). For example, work from our laboratory showed
537 that there is a 12-18 ms reduction in the corticospinal silent period following both upper-
538 (Coombs et al. 2016; Kidgell et al. 2015; Latella et al. 2012; Mason et al. 2017a) and lower-
539 limb cross-education (Goodwill et al. 2012; Latella et al. 2012). There is also good evidence
540 that shows SICI is reduced (Goodwill et al. 2012; Hendy et al. 2015; Kidgell et al. 2015),
541 suggesting cross-education selectively reduces the synaptic efficacy of inhibitory networks
542 within the ipsilateral M1 and corticospinal tract. Because the corticospinal silent period is
543 modified by $GABA_B$-mediated inhibition (Werhahn et al. 1995), it seems that cross-education
544 specifically affects intracortical inhibitory neurones that collectively results in an improved
545 ability to activate the spinal motorneurone pool, which could partly explain the increases in
546 muscle strength.

547 The reduced corticospinal silent period and SICI show that the GABA-ergic inhibitory
548 neural networks are important for maximal force generation and are associated with the cross-
549 education of muscle strength (Christie and Kamen 2013; Coombs et al. 2016; Kidgell and
550 Pearce 2010; Weier et al. 2012). This line of enquiry is supported by early theories of cross-
551 education whereby reductions in IHI could play a pivotal role in the behavioural effects
552 observed (Hellebrandt 1951; Hortobágyi et al. 2011). The reduction in corticospinal inhibition
553 seems to be an important mechanism that mediates cross-education because several studies,
554 that have used models of immobilization, have reported increased silent-period durations and
555 reduced muscle-strength (Clark et al. 2008; Pearce et al. 2012); however, motor training seems
556 to attenuate the prolongation of the corticospinal silent period (Clark et al. 2014).

557 The reduction in SICI following cross-education suggests that the excitability of short-
558 latency intracortical inhibitory circuits are reduced, which serves to focus the excitatory drive
559 onto corticospinal neurones within the ipsilateral M1 that produce the intended movement of

560 the agonist muscle (Reynolds and Ashby 1999; Ridding et al. 1995). Certainly, evidence is
561 now available that, during increased muscle activity, the reduction in inhibition is selective and
562 specific to the agonist muscle. This supports the findings of Mason et al. (2017a) whereby
563 ipsilateral changes in inhibition were confined to the agonist muscle following cross-education.

564 To date, there has only been one cross-education study that has examined LICI (Manca
565 et al. 2016a). Participants trained the first dorsal interosseous (FDI) muscle via a maximal
566 pinch-force task (five sets of ten repetitions) three days a week for four-weeks. Following
567 training, there were no changes in LICI, but the corticospinal silent period was not measured.
568 Based upon the current systematic evidence available, in order to increase our understanding
569 of the corticospinal responses to cross-education, there is a need to design cross-education
570 studies that use techniques to probe both the excitatory and inhibitory cortico-cortical
571 connections following both acute and chronic interventions. These will provide important
572 information about the mechanisms associated with cross-education.

573 ***Interhemispheric inhibition and cross-education***

574 TMS can be used to assess the mediating inhibitory pathways between cerebral
575 hemispheres via IHI. IHI is a neurological mechanism whereby one hemisphere inhibits the
576 opposite hemisphere and its presence is due to excitatory pathways via the corpus callosum
577 which synapse onto local inhibitory circuits within the target M1 (Perez and Cohen 2009).
578 Eight-weeks of maximal isometric training of the right FDI reduced IHI from the trained to the
579 untrained M1 by 31% and, importantly, this increase was associated with the magnitude of
580 cross-education (Hortobágyi et al. 2011). This finding supports the evidence from the
581 examination of IHI following strong unilateral contractions and acute motor-skill training
582 (Hortobágyi et al. 2003; Perez et al. 2007c). However, Manca et al. (2016a) recently reported
583 that four weeks of cross-education had no effect on IHI. Currently, it is inconclusive whether

584 reductions in IHI mediate cross-education, but the physiological role of IHI seems to be an
585 important modulator for cross-education. For example, one hypothesis suggests that reduced
586 IHI from the trained to the untrained M1 would support the theory of cross-activation from the
587 active to the non-active M1 (Lee et al. 2010), a mechanism consistently reported during
588 maximal contraction of one limb (Hortobágyi et al. 2003) and implicated in cross-education
589 (Frazer et al. 2017; Hendy and Kidgell 2014; Hendy et al. 2015; Mason et al. 2017a; Ruddy et
590 al. 2017).

591 Collectively, the use of TMS to examine the ipsilateral corticospinal responses to cross-
592 education has begun to provide some putative neural mechanisms that mediate a change in
593 strength of an untrained limb. However, there is a need to establish whether there is a direct
594 relationship between the changes in ipsilateral corticospinal responses and the magnitude of
595 cross-education. Thus, at present, it remains tentative whether the changes in ipsilateral TMS
596 responses actually underpin the observed changes in strength of the untrained limb.
597 Furthermore, because of the limitations associated with TMS and the anatomy of the
598 corticospinal tract, changes in the excitability of the spinal cord and the ability to activate the
599 motoneurone pool (i.e., voluntary activation) may also add further insights into the ipsilateral
600 corticospinal responses associated with cross-education.

601

602 **Potential spinal mechanisms and cross-education**

603 There is evidence to suggest that adaptations in spinal circuitry occur following strength
604 training (Duclay et al. 2008); however, current methodology is unable to determine specific
605 spinal pathways that may be involved in the cross-education of strength (Dragert et al. 2011;
606 Fimland et al. 2009; Lagerquist et al. 2006). Despite this, the Hoffman reflex (H-reflex), an
607 electrically evoked reflex used to quantify the efficacy of the 1a afferent motoneuronal synapse

608 (Palmeri et al. 2004), has been measured in only three cross-education studies (Dragert et al.
609 2011; Fimland et al. 2009; Lagerquist et al. 2006). All three studies showed no change in H-
610 reflex amplitude following cross-education. Thus, these findings do not enable any definitive
611 conclusions to be drawn as to whether the intrinsic circuitry of the spinal cord contributes to
612 the cross-education of strength.

613

614 **Twitch force studies and cross-education**

615 The interpolated twitch technique has been used extensively to measure voluntary
616 activation as a reflection of "neural drive" (Merton 1954). In addition to measuring sEMG
617 changes with unilateral and contralateral musculature following training, twitch interpolation
618 (or interpolated twitch technique) is a single-pulse protocol that allows investigations to
619 address the question of training protocols increasing central nervous system excitability. In
620 particular, twitch interpolation allows for the investigation of whether the motoneurone pool
621 has been excited sufficiently by volition to evoke all the force the relevant muscle can produce
622 (Herbert and Gandevia 1999; Gandevia, 2001; Todd et al. 2016). The amplitude of the
623 interpolated twitch declines with increasing contraction intensity (voluntary activation)
624 allowing for the quantification of the level of excitation of motoneurones, or "neural drive"
625 (Herbert and Gandevia 1999).

626 Historically, understanding the neural mechanisms contributing to strength changes
627 following strength training has been conducted in the primary agonist muscle (see review by
628 Shield and Shi 2004). However, electrical twitch interpolation has also been used to assess
629 neural adaptation in contralateral neural pathways following unilateral strength training (cross-
630 education; see Table 3). For example, Shima et al. (2002) showed that, in healthy untrained
631 males (n=9), voluntary activation increased in both trained and contralateral untrained leg

(plantar flexor muscles) following a six-week training period of progressive strength training of calf raises and foot-presses. Moreover, following a six-week period of detraining, the authors found that voluntary activation did not significantly change (trained: 0.3 ± 2.6%; contralateral: -0.7 ± 1.7%), suggesting that cross education of muscular strength might be explained by central neural mechanisms during training and, at least in part, during the period of detraining (Shima et al. 2002).

More recently, twitch interpolation has been used to assess neural adaptations with strength training in older populations (Tøien et al. 2017). Whilst it is known that age can attenuate efferent neural drive, even in those with a long history of strength training experience, these authors investigated whether the deterioration of neural drive impedes contralateral neural drive with increasing age (Molenaar et al. 2013). They used an older population of males (n = 23; mean age 73 ± 4 years) who undertook a three-week strength training program (nine sessions; three sessions per week) of dynamic plantar flexion involving both concentric and eccentric contractions (90% of one-repetition maximum [1RM]). Voluntary activation, measured in the contralateral soleus muscle, increased by a mean of 5.0 ± 5.5%. Tøien et al. (2017) suggested that older individuals exhibit cross-limb neural adaptations, providing a potential clinical value in unilateral high-intensity strength-training that is not limited by age.

Whilst the majority of studies using interpolated twitch technique are undertaken electrically, magnetic stimulation may also be used (Lampropoulou et al. 2012). Since 2000, there has been increased interest in using peripheral magnetic stimulation as an alternative to electrical stimulation in assessing voluntary activation (Goodall et al. 2014) in upper-limb (Harris et al. 2000; Lampropoulou et al. 2012) and lower-limb musculature (Goodall et al. 2009; Hamnegård et al. 2004; Kremenic et al. 2004; Vivodtzev et al. 2005). Comparisons between electrical and magnetic peripheral twitch interpolation during maximal voluntary contractions show similarities in the onset latencies and supramaximal twitch response in hand muscles

(Harris et al. 2000; Olney et al. 1990) and also in biceps brachii (Lampropoulou et al. 2012). However, peripheral twitch interpolation is limited because the exact level (or site) of adaptation within the central nervous system cannot be distinguished as the change may occur at any point, or combination of points, proximal to the position of stimulation (Goodall et al. 2014). Further, it has been argued that other limitations of peripheral stimulation, including the strength of the stimulus, can pose problems in terms of the distribution of the magnetic field, particularly if it is too high (supramaximal stimulus) and the spread of the magnetic field can conduct to tissues other than the target peripheral nerve (Hamnegård et al. 2004; Matsumoto et al. 2010; Millet et al. 2011). Conversely, the stimulus might not be of sufficient intensity if the coil position is not correctly orientated (Lampropoulou et al. 2012) to maximally stimulate all motor units, a desired outcome that might also be limited by subcutaneous adipose tissue (Lin et al. 2008; Tomazin et al. 2010, 2011). As a result, peripheral magnetic stimulation does not have extensive recognition either as a 'gold standard' technique or as a practical alternative to electrical twitch interpolation (Lampropoulou et al. 2012).

Magnetic stimulation has also been shown to elicit a twitch response when stimulation is applied over the M1. There are many studies that utilise TMS to quantify adaptations of the corticospinal pathway following short-term strength-training, not only in the trained (Kidgell and Pearce 2010; Kidgell et al. 2010; Leung et al. 2017; Mason et al. 2017b; Weier et al. 2012) but also in the untrained contralateral arm (Coombs et al. 2016; Kidgell et al. 2011, 2015) and leg (Goodwill and Kidgell 2012; Goodwill et al. 2012; Latella et al. 2012). However, these studies generally used sub-maximal contractions to measure MEPs and corticospinal silent period as determinants of neural adaptations in the contralateral untrained limb. While maximal voluntary activation of human elbow-flexors can be assessed with TMS (VA_{TMS}) (Todd et al. 2004), few studies have employed the technique of VA_{TMS} to assess the neural adaptations to cross-education (Lee et al. 2009b). This is surprising because an advantage of VA_{TMS} is that it

allows the assessment of supraspinal contributions for the volitional drive to the muscle during a maximal contraction (Lee et al. 2008). However, the technique itself is technically difficult and has its own limitations. For example, it is imperative that the TMS stimulus produces a maximal response in the target muscle (Carroll et al. 2008). In addition, changes in VA_{TMS} are likely to be more specific to the testing condition (e.g., isometric), thus training interventions that do not match the conditions of testing prove problematic when interpreting the data.

Despite the theoretical contribution of VA_{TMS}, there is a paucity of research using this technique, particularly for contralateral neural adaptations following cross-education strength training. To date, only one study has utilized TMS twitch interpolation to assess neural adaptations in the contralateral arm (Lee et al. 2009b). Following four weeks of unilateral wrist extension strength training, a significant increase in contralateral voluntary activation in the untrained wrist was observed (2.9 ± 3.5%). These authors concluded that unilateral maximal strength training improved motor output from the M1 to the homologous untrained muscles. Given the potential of using VA_{TMS} to assess the ability of the M1 to drive the motoneurone pool, future studies should consider incorporating this technique.

Interventions to enhance the cross-education effect

Recently, there have been some innovative techniques used to enhance the cross-education effect. There is now some preliminary evidence to show that the cross-education of strength may be enhanced by mirror feedback. This intervention activates the mirror neuron system (MNS) which is known to have projections to motor regions (Zult et al. 2014). In addition, there are emerging studies that have used tDCS, a simple and cost effective technique whereby electrodes are placed over the M1 of a target muscle and low levels of electricity are passed through to the underlying cortical neurones (Frazer et al. 2017). Both acute and chronic

706 studies now show that the cross-education of strength is enhanced when tDCS is applied to the
707 ipsilateral M1 before or during the training intervention (Frazer et al. 2017; Hendy and Kidgell
708 2014; Hendy et al. 2015). In a similar manner, applying electrical stimulation over the training
709 muscles (Hortobágyi et al. 1999) and whole-body vibration training (WBV) have also been
710 used to enhance the cross-education effect (Goodwill and Kidgell 2012; Lapole et al. 2013).

711 ***Mirror neurones and mirror box training to augment cross-education***

712 The aforementioned work reporting cross-education of strength is compelling. When
713 coupled with evidence showing that this phenomenon can attenuate strength loss and reduce
714 the magnitude of atrophy during short-term immobilisation in healthy individuals with
715 (Magnus et al. 2013) and without (Farthing et al. 2009, 2011; Pearce et al. 2012) a fracture,
716 this opens up exciting possibilities for cross-education as a therapeutic intervention in clinical
717 populations with unilateral orthopaedic and neurological dysfunction. These preliminary data
718 are promising, but many clinical populations have unilateral dysfunction for periods of time
719 more extended than those studied in the literature. Consequently, cross-education might not be
720 as efficacious in some scenarios. Given the potential clinical importance of cross-education, it
721 would be of interest to explore methods that have the potential to further augment the
722 magnitude of the cross-education of muscle strength. Because sensory feedback during motor
723 practice can increase motor output, one possibility is to activate neurones involved in the
724 transfer that might also be activated by other means, thereby resulting in a synergistic effect on
725 motor output and, hence, increase the transfer of strength (Howatson et al. 2013).

726 Previous research (Carson and Ruddy 2012; Farthing et al. 2007, 2011; Hortobágyi et
727 al. 2011) has shown that, following strength training and the subsequent cross-education, there
728 is overlap in the activation of brain areas that contain mirror neurones. The MNS is a network
729 of neurones that are active during perceptual and actual execution of motor activities (Iacoboni
730 1999, 2005; Rizzolatti et al. 1996). In a recent hypothesis (Howatson et al. 2013) and systematic

731 review (Zult et al. 2014), the possibility of activating the MNS concurrently with performing a
732 cross-education strength task was proposed to increase the magnitude of cross-education.

733 The MNS is distributed across numerous areas of the cerebral cortex and provides a
734 neuroanatomical basis for 'action observation' whereby observation and/or imitation of an act
735 can develop motor learning and skill acquisition (Rizzolatti et al. 1999; Sakadjian et al. 2014).
736 In brief, it is thought that the MNS is activated when performing a similar task that has been
737 observed. Specifically, the MNS is activated during the observation of a self-performed act,
738 observing a third person, imitation of an observed task, perceptual input and the performance
739 of the practised movement (di Pellegrino et al. 1992; Heyes 2010; Ray and Heyes 2011). These
740 activities are very common in the arts and athletic performance where extensive observed
741 practice is used to master skills that stimulate areas common to motor cortical areas and the
742 MNS which are detailed elsewhere (Howatson et al. 2013; Zult et al. 2014). Previous
743 experience of the motor activity seems important to modulate and engage the MNS (Beudel et
744 al. 2011); naïve participants, when compared to skilled dancers and musicians, show greater
745 MNS activation when observing dancers and musicians, respectively (Heyes 2010). Therefore,
746 practice of a task will likely engage these neural networks and improve motor performance
747 (Howatson et al. 2013; Zult et al. 2014).

748 Conceptually, the observation of a relatively simple, self-performed, unilateral motor-
749 task (like resistance exercise) might enhance the cross-education effect by viewing the
750 performed task in a mirror. In this concept, a reflected image (with the use of a mirror) is
751 superimposed over the non-exercising limb to provide the illusion that the non-active limb is
752 moving. The reality is that the participant is actually viewing a reflection of the exercising limb
753 and, hence, receives the visual sensation of the non-active limb actually moving (Nojima et al.
754 2012; Small et al. 2012). Previous work using mirror training showed increased ipsilateral brain
755 activity (Garry et al. 2005; Matthys et al. 2009), skill acquisition of the non-practised hand in

healthy participants (Hamzei et al. 2012; Läppchen et al. 2012; Nojima et al. 2012), reduced phantom-limb pain (Ramachandran and Rogers-Ramachandran 1996), and enhanced stroke recovery (Sütbeyaz et al. 2007; Yavuzer et al. 2008). The brain structures thought to be implicated in cross-education have neuroanatomical commonality with those of the MNS. This makes the expectation tenable that observing the moving limb in a mirror could increase the brain activity controlling the resting limb and, thereby, increase the magnitude of cross-education (Howatson et al. 2013; Zult et al. 2014). Until recently, this idea had not been explored experimentally.

In two subsequent studies arising from the aforementioned concept, we explored the cortical excitability and intra and interhemispheric connectivity: 1) when observing forceful contractions in a mirror; and 2) to assess the magnitude of cross-education when resistance training was performed using a mirror. The first of these studies (Zult et al. 2015) was cross-sectional in nature to examine the cortical networks hypothesised to share commonality between the MNS and networks thought to be involved in cross-education. In this work, 27 right-handed male volunteers had corticospinal and motor-cortical responses to TMS recorded in the left flexor carpi radialis (FCR). This was done with and without viewing a mirror, at rest and during a forceful shortening contraction of the right-wrist flexors. Corticospinal excitability in the resting FCR increased during the contraction (similar to that observed previously) but was not different between mirror and no-mirror conditions. However, SICI was significantly lower (~9% release of SICI) illustrating that GABA-ergic inhibitory networks were implicated in the cross-education phenomenon (Goodwill et al. 2012; Perez and Cohen 2008). This first step in support of the hypothesis (Howatson et al. 2013) provided evidence that neural networks implicated in cross-education can also be modulated by viewing a reflection of the exercising limb superimposed on the resting limb. In a follow-up training study that further tested this idea, Zult and colleagues (2016) took 24 right-handed volunteers to

781 undertake either mirror training or no-mirror training. Specifically, all participants completed
782 15 resistance-training bouts (six sets of eight repetitions isokinetic, concentric actions [20°/s]
783 at 80% MVC) of the right-wrist flexors over a three-week period. Critically, the training
784 resulted in improved performance in both groups, but the mirror group had a 13% greater
785 increase ($P = 0.03$) than the no-mirror group in strength of the untrained limb. These strength
786 improvements in the untrained limb were accompanied with a mean reduction in the
787 contralateral silent period of 30 ms, which was thought to be indicative of greater inhibition of
788 $GABA_B$-mediated networks. In addition, there were reductions in interhemispheric inhibition,
789 a GABA-ergic network between cortical hemispheres which is also implicated in the MNS
790 from a neuroanatomical perspective (Zult et al. 2014).

791 Although the potential for using a mirror to augment the cross-education effect is just
792 emerging, it provides a potentially exciting field of research. Volunteers in these studies (Zult
793 et al. 2015, 2016) verbally reported sensations of the left, non-active limb moving when
794 observing strong monotonic contractions of the right limb in a mirror that were superimposed
795 on the non-active limb. So, conceptually, there could be a placebo effect that has limited the
796 neurophysiological basis (at least in the measure collected). Notwithstanding, these data are
797 particularly important because of the implications for clinical populations, whereby an increase
798 in the cross-education phenomenon is amplified. This effect should be investigated further to
799 explore its application to unilateral orthopaedic or neurological impairment. Importantly, the
800 use of neuroimaging techniques to establish the role of the MNS and other regions of the
801 cerebral cortex seems to be an important progression in understanding the mediating
802 mechanisms of cross-education (Rizzolatti and Craighero 2004).

803 ***Transcranial direct current stimulation and cross-education***

804 tDCS has emerged as a promising, non-invasive technique to improve motor
805 performance in both young and older adults (Goodwill et al. 2015; Kidgell et al. 2013). The
806 application of tDCS over the M1 induces transient, polarity-specific changes in the neuronal
807 resting membrane potential (Nitsche et al. 2008), with increases in excitability and performance
808 improvements lasting up to 90 min following the cessation of stimulation (Lang et al. 2005).
809 However, similar to the TMS strength-training studies (Kidgell et al. 2017), the reproducibility
810 of neuroplasticity inducing protocols, like tDCS, remains a challenge (Heroux et al., 2015;
811 Heroux et al., 2017). However, recently, tDCS has been used experimentally to enhance the
812 cross-education of muscle strength. For example, Hendy and Kidgell (2014) reported an
813 increase in maximal strength and cross-activation of the contralateral untrained limb (left hand)
814 following a single session of anodal tDCS applied to the ipsilateral right M1 during strength
815 training of the right hand (Hendy and Kidgell 2014). In a follow-up study, Hendy et al. (2015)
816 applied anodal tDCS to the ipsilateral right M1 during a two-week strength-training
817 intervention and showed that the effects of cross-education were prolonged, and that tDCS
818 retained strength of the untrained limb compared to sham tDCS and strength-training (Hendy
819 et al. 2015).

820 Although this data is interesting and has potential applications in the clinical
821 environment, there is a greater need to identify the optimal timing of tDCS to the ipsilateral
822 M1 (i.e., before, during or after training). In an attempt to address this, we recently
823 demonstrated a substantial increase in maximum strength of the untrained left biceps brachii
824 when anodal tDCS was applied to the ipsilateral M1 (right hemisphere), prior to a single bout
825 of strength training of the right arm only, exploiting the principles of homeostatic meta-
826 plasticity (Frazer et al. 2017). Although preliminary evidence indicates that tDCS is a
827 promising tool, the timing of application needs to be rigorously investigated following both
828 single-session and longer-term training periods (>2 weeks). Undoubtedly, combining robust

investigation techniques, such as TMS and fMRI, would aid in quantifying the potential opportunity to augment the cross-education of muscle strength.

Electromyostimulation during cross-education

Similar to voluntary contractions evoked during unilateral strength training, there is good evidence to show that the application of electrostimulation during strength training increases MVC force production of an untrained homologous muscle following unilateral strength training (Bezerra et al. 2009; Hortobágyi et al. 1999). There are now several studies that have revealed electrical stimulation of a muscle, compared with voluntary contraction, evokes specific effects at the level of the cerebral cortex and increases force in an untrained limb (Bezerra et al. 2009; Hortobágyi et al. 1999). Hortobágyi et al. (1999) reported that electrical muscle stimulation induced a contralateral increase in strength of 21% following four-weeks of isometric strength training, which was comparable to that induced by voluntary isometric strength training alone. In addition, six weeks of eccentric strength training with electrical muscle stimulation induced an increase in strength of 104% compared to 23% for voluntary eccentric training alone (Hortobágyi et al. 1999; Oakman et al. 1999). Interestingly, electrical stimulation training is also more effective than voluntary strength training when imparting a cross-education effect (Bezerra et al. 2009). Because the cross-education effect following electrical stimulation training is not associated with any changes in the cross-sectional area of the contralateral untrained muscle (Bezerra et al. 2009), the physiological mechanisms underpinning the changes in strength seem to reside within the cerebral cortex. For example, when electrical muscle stimulation is used to induce left-wrist flexion, both TMS induced MEPs and the H-reflex increase in the right resting-wrist flexors (Hortobágyi et al. 2003). In a similar manner, when electrical muscle stimulation is applied during voluntary contraction of the left-wrist flexors, TMS-induced MEPs are increased, but the H-reflex in the right resting-wrist flexors is reduced (Hortobágyi et al. 2003). These observations suggest that

854 electrical muscle stimulation and voluntary contractions are affected differently at a supraspinal
855 level in contralateral homologous muscles. This difference is likely the result of increased
856 sensory and nociceptive inputs that act at a cortical level following electrical stimulation.
857 Perhaps such inputs modify motor output and interhemispheric paths, which lead to an increase
858 in strength of the trained and untrained limb. Certainly, this hypothesis is supported by changes
859 in IHI following unilateral training (Hortobágyi et al. 2011; Howatson et al. 2011; Lee et al.
860 2010).

861 ***Whole-body vibration training and cross-education***

862 The recent emergence of WBV as a training technique has been of interest to
863 researchers due to its potential to improve neuromuscular function. Many studies have reported
864 increases in strength following an acute bout of WBV. Similarly, increases in strength have
865 also been demonstrated following a period of strength training with the addition of WBV
866 (Issurin 2005; Nordlund and Thorstensson 2007; Rittweger 2010), suggesting that WBV
867 training may be an effective and alternative training technique for strength development
868 (Rittweger et al. 2003) and for enhancing cross-education (Goodwill and Kidgell 2012). Given
869 that the magnitude of strength gain in the trained limb is an important proxy for strength transfer
870 to the untrained limb, we recently examined the effect of unilateral strength training with
871 superimposed WBV on the magnitude of cross-education (Goodwill and Kidgell 2012).
872 Healthy participants completed unilateral strength training with or without the application of
873 WBV (35 Hz; 2.5 mm amplitude), three times per week for three weeks. Strength increased by
874 41% in the trained limb following strength training without WBV and by 55% with WBV.
875 Interestingly, the cross-transfer of strength was greater for the untrained limb (52%) following
876 WBV, with only a 35% transfer following training without WBV. Further, after WBV training,
877 there was an increase in corticospinal excitability and a reduction in SICI of the ipsilateral M1
878 suggesting that WBV training had a cortical effect (Goodwill and Kidgell 2012). In a similar

manner, 14 days of Achilles-tendon vibration also increased the strength of a vibrated gastrocnemius and the non-vibrated gastrocnemius muscle. The increase in strength of the non-vibrated gastrocnemius was associated with a 41% increase in the volitional wave (a measure of neural drive), but the H-reflex remained unchanged (Lapole et al. 2013). These observations suggest that there could be additional cross-education benefits following the application of vibration to the training limb.

Clinical application of cross-education

In clinical practice, unilateral injuries, such as knee osteoarthritis, tendinopathy, fracture, stroke, and cerebral palsy are extremely common. In the Western world, 6% of women will have sustained a distal radius fracture by the age of 80, and 9% by the age of 90. Regardless of whether these fractures are treated surgically or by casting, patients are immobilised for two to six weeks (or more). Physical and occupational therapy, as a key element in rehabilitation, typically only starts following the period of immobilisation. During the period of immobilisation, patients often keep their injured limb in rigid postures, and the involved ligaments of the joints become shortened (Freeland and Luber 2005). Different methods of treatment, but especially the long immobilisation periods, lead to a high incidence of complications which are typically associated with poor functional outcomes (McKay et al. 2001). These complications include complex and regional pain syndrome, stiffness, nerve injury, tendon and ligament injuries, and a large reduction in range of motion and muscle strength (Diaz-Garcia et al. 2011). In addition, recovery of the strength loss and muscle atrophy experienced following a unilateral injury and period of immobilisation is often hampered by patients' and therapists' inability to effectively exercise the involved body part. As a result, final function of the injured limb is often suboptimal, highlighting the critical need to

903 implement strategies such as cross-education to attenuate the loss of function that occurs with
904 immobilisation.

905 Although there is a strong consensus that unilateral motor practice is a viable candidate
906 to reduce unilateral loss of muscle strength and motor function during a period of
907 immobilisation, there is limited evidence to support this notion. To date, just five studies have
908 investigated the effects of cross-education in healthy participants undergoing a period of
909 immobilisation (Andrushko et al. 2017; Farthing et al. 2009, 2011; Papandreou et al. 2013;
910 Pearce et al. 2012). All five investigations found that a cross-education intervention attenuated
911 the strength loss in the immobilised limb, with four of the investigations also displaying a
912 sparing effect for muscle size (Andrushko et al. 2017; Farthing 2009; Papandreou et al. 2013;
913 Pearce et al. 2012). Of particular interest, this cross-education model was successfully
914 translated into a clinical population of women older than 50 years who suffered a unilateral
915 distal radius fracture (Magnus et al. 2013). Magnus et al. (2013) demonstrated an increase in
916 strength and range of motion of injured wrists 12-weeks post-fracture, providing preliminary
917 evidence of the clinical efficacy of cross-education for immobilised patients. Nevertheless,
918 there is still insufficient empirical evidence demonstrating that unilateral training of the non-
919 injured limb during the early rehabilitation period can attenuate atrophy and strength loss
920 associated with immobilisation. The successful implementation of such an intervention, and
921 subsequent exploitation of the cross-education effect, could accelerate recovery by enabling
922 patients to maintain a higher level of function in the injured limb prior to remobilisation. This
923 would have the dual benefit of improving functional outcomes in the immediate period post-
924 injury and facilitating the execution of rehabilitation exercises designed to mobilise, reduce
925 atrophy and strengthen the injured limb.

926 Another highly-plausible application of cross-education is the restoration of bilateral
927 limb symmetry following stroke (Dragert and Zehr 2013). A recent meta-analysis has shown

928 the positive effect of cross-education on muscle strength in patients who have suffered a stroke
929 (Ehrensberger et al. 2016). Although only two studies were analysed, post-stroke hemiplegic
930 patients demonstrated a 31.4% and 45.5% strength increase in the untrained, more-affected
931 dorsiflexor muscle following unilateral training (Dragert and Zehr 2013; Kim et al. 2015).
932 Indeed, these results are promising; however, attention needs to shift beyond the focus of
933 demonstrating a transfer in strength to gains in functional tasks and recovery of motor function
934 (Ehrensberger et al. 2016). Furthermore, there has been recent preliminary evidence suggesting
935 that cross-education might aid in the management of limbs severely weakened because of
936 multiple sclerosis (Dragert and Zehr 2013; Manca et al. 2016b, 2017b). Of note, none of the
937 trials investigating the efficacy of cross-education in neurological patients employed a training
938 design using eccentric or dynamic contraction modes. Given the recent finding that eccentric
939 and dynamic contractions induce significantly greater contralateral gains in strength in healthy
940 subjects (Manca et al. 2017a), it would be interesting to examine whether the transfer of
941 strength in neurological subjects may be further enhanced by changing the type of training
942 contraction employed. This highlights the urgency to not only investigate the role of cross-
943 education in the rehabilitation and management of neurological patients, but also to further
944 enhance our understanding of best prescription variables for this population. Overall, there is a
945 great need to examine the efficacy of cross-education in clinical populations with an emphasis
946 on using interventions which are known to maximise the cross-education effect.

947

948 **General summary and conclusions**

949 Cross-education is a phenomenon that has been shown to occur following different
950 unilateral strength-training interventions. Although some variability exists regarding the
951 magnitude of the cross-education effect between the upper and lower limbs, critically, there is

952 a lack of correlation between the reported cross-education effect and the changes in the nervous
953 system. Overall, it seems that the neural adaptations to cross-education of muscular strength
954 most likely represent a continuum of change within the central nervous system that involves
955 both structural and functional changes within cortical motor and non-motor regions. Such
956 changes are likely to be the result of more subtle changes along the entire neuroaxis which
957 include increased corticospinal excitability, reduced cortical inhibition, reduced IHI, changes
958 in VA_{TMS} and new regions of cortical activation (see Fig. 1).

959 ***Insert Figure 1.***

960 Notwithstanding, there is a need to widen the breadth of research that collectively
961 employs several neurophysiological techniques to better understand the potential mechanisms
962 mediating cross-education. This fundamental step is required in order to better prescribe
963 targeted and effective guidelines for the clinical practice of cross-education. There is a need to
964 determine whether similar cortical responses also occur in clinical populations where, perhaps,
965 the benefits of cross-education could be of most benefit.

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967

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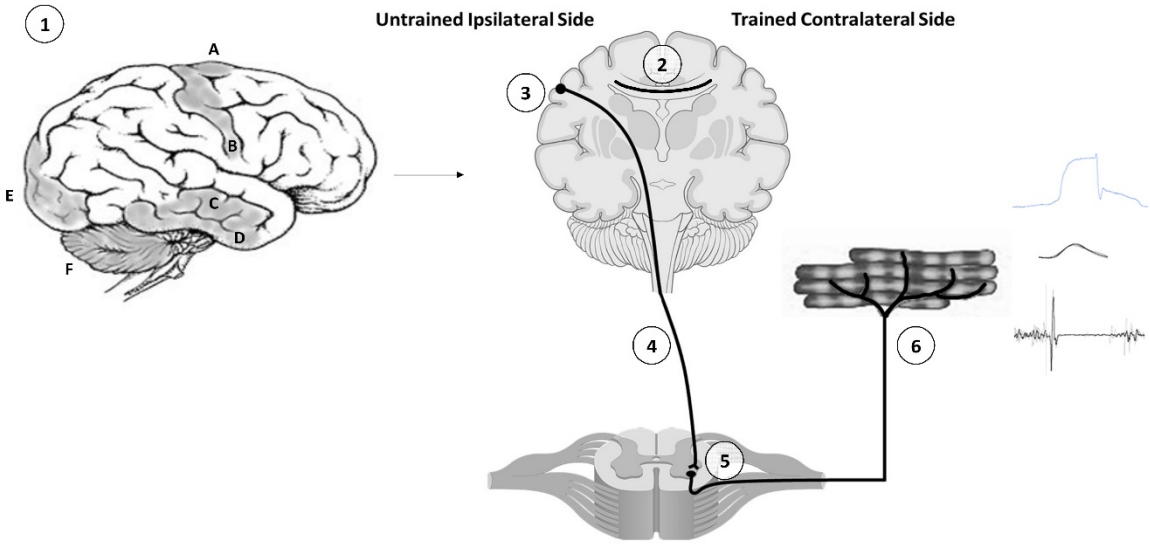
Figure 1. Potential sites of neural adaptation to cross education include **(1)** changes in (A) supplementary motor area, (B) primary motor cortex, (C) middle temporal gyrus, (D) inferior temporal gyrus, (E) occipital lobe, (F) cerebellum, **(2)** changes in interhemispheric inhibition, **(3)** changes in TMS measures confined to the ipsilateral "untrained" primary motor cortex (SICI), **(4)** changes along the corticospinal tract ipsilateral to the trained limb (excitability and inhibition), **(5)** changes in motoneurone excitability, and **(6)** changes in VA_{TMS}, raw EMG response (MEP) produced by cortical stimulation during maximal contraction, as well as the superimposed twitch produced by cortical stimulation during maximal contraction, (right).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A
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Untrained Ipsilateral Side
Trained Contralateral Side
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Table 1: Summary of studies examining the effect of unilateral motor-training on structural connectivity and patterns of brain activation.

Study	Subject Details	Muscle Group	Methods	Training Details	Training Intensity	Strength Gain	Results
Ruddy et al. 2017	44 subjects (20 control, 24 experimental)	Wrist flexors	rs-fMRI and DWI	One session	300 'fast as possible' wrist flexion	↑ 83% peak acceleration	↑rs-fMRI of right/left SMA; DWI was associated with increased transfer
Farthing et al. 2007	23 subjects (12 physical training, 11 imagery)	Flexor Carpi Ulnaris	fMRI patterns of activation, maximal isometric muscle activation (EMG)	6 wks of unilateral isometric training	Isometric MVC 6 × 8 reps	↑ 47.1% MVC	↑ muscle activation ↑ activation M1 and SMA, left ventral M1 and SMA, left anterior and posterior middle temporal gyrus, left inferior temporal gyrus, medial occipital cortex and posterior medial and lateral cerebellum

DWI: diffusion weighted imaging; **EMG:** electromyography; **M1:** motor cortex; **MVC:** maximum voluntary contraction; **rs-fMRI**: resting-state functional magnetic resonance imaging; **SMA:** supplementary motor area; **wks:** weeks

Table 2: Summary of studies examining the effect of cross-education training on cortical excitability and inhibition.

Study	Participant Details	Muscle Group	Training Details	TMS Method	TMS Outcome for untrained limb
Hortobágyi et al. 2011	20 participants (12 trained, 8 control)	First dorsal interosseous	5 × 10 MVCs performed at 80%, 3/wk × 8 wks	MEPs, SICI, ICF & IHI during 20 and 80% MVC	↑ MEPs at 20 and 80% MVC, ↓IHI
Kidgell et al. 2011	26 participants (13 trained, 13 control)	Biceps brachii	4 × 6-8 bicep curls at 80% 1-RM, 3/wk × 4 wks	MEPs and CSP during 10%*rms*EMG	↑ MEPs during, ↔ CSP
Latella et al. 2012	18 participants (9 trained, 9 control)	Rectus Femoris	3 × 8 leg presses at 78%-88.5% 1-RM, 3/wk × 8 wks	MEPs and CSP during 10%*rms*EMG	↔ MEPs during 10%*rms*EMG, ↓CSP
Goodwill et al. 2012	14 participants (7 trained, 7 control)	Rectus Femoris	4 × 8 single-leg squats at 80% 1-RM, 3/wk × 4 wks	MEPS and SICI during 10% MVC	↑ MEP_{max}, ↓SICI
Kidgell et al. 2015 (concentric)	18 participants (9 trained, 9 control)	Wrist flexors	4 × 8 maximal concentric wrist flexion performed at 20°/s	MEPs, SICI and CSP during 5, 20 and 40% MVC and 40%	↔MEPs at 5, 20 & 40% MVC, ↔SICI at 5, 20 & 40% MVC, ↔CSP at 5, 20 & 40% MVC
Kidgell et al. 2015 (eccentric)	18 participants (9 trained, 9 control)	Wrist flexors	4 × 8 maximal eccentric wrist flexion performed at 20°/s	MEPs, SICI and CSP during 5, 20 and 40% MVC and 40%	↑MEPs at 40% MVC, ↓SICI at 40% MVC, ↓CSP at 5 & 20% MVC
Coombs et al. 2016 (right-hand)	15 participants (8 trained, 7 control)	Wrist extensors	4 × 6-8 wrist extensions at 70% 1-RM for the right arm only	MEPs, SICI and CSP during 5%*rms*EMG	↔MEPs, ↔SICI, ↓CSP at MEP_{max}
Coombs et al. 2016 (left arm)	15 participants (8 trained, 7 control)	Wrist extensors	4 × 6-8 wrist extensions at 70% 1-RM for the left arm only	MEPs, SICI and CSP during 5%*rms*EMG	↔MEPs, ↔SICI, ↔CSP
Manca et al. 2016a	24 subjects (17 trained, 17 control)	First dorsal interosseous	5 × 10 isometric pinch contractions, 3/wk × 4 wks	MEPs at rest and during 10% MVC, SICI, ICF, SICF, SIHI and LICI	↔MEPs, ↔SICF, ↔SICI, ↔ICF, ↔LICI, ↔SIHI and ↔ LIHI
Mason et al. 2017b	20 participants (10 trained, 10 control)	Biceps brachii	4 × 6-8 bicep curls at 80% 1-RM, 3/wk × 3 wks	MEPs and CSP during 5%*rms*EMG	↑MEPs and ↓CSP

1-RM: one-repetition maximum; **CSP:** cortical silent period; **ICF:** intracortical inhibition; **IHI:** interhemispheric inhibition; **LICF:** long-interval intracortical facilitation; **LICI:** long-interval intracortical inhibition; **MEP:** motor evoked potential; **MVC:** maximum voluntary contraction; **SICF:** short-interval intracortical facilitation; **SICI:** short-interval intracortical inhibition, **wk:** week; **wks:** weeks

Table 3: Summary of studies examining the effect of cross-education training on voluntary activation of the untrained limb.

Study	Participant Details	Muscle Group	Training Details	Twitch Method	Twitch Outcome
Lee et al. 2009b	20 participants (10 trained, 10 control)	Wrist extensors	4 × 10 brief (1-2 s) isometric wrist extension, 3/wk × 4 wks	TMS cortical voluntary activation	↓ superimposed twitch evoked during extension MVC
Shima et al. 2002	15 participants (9 trained, 6 control)	Gastrocnemius	3 × 10-12 reps at 70-75% 1-RM, 4/wk × 6 wks	Interpolated twitch technique	↔voluntary activation
Tøien et al. 2017	23 participants (11 trained, 12 control)	Gastrocnemius	4 × 4 reps at 90% 1-RM, 3/wk × 3 wks	Interpolated twitch technique	↑ voluntary activation
Fimland et al. 2009	26 participants (15 trained, 11 control)	Gastrocnemius	7 ×1 min isometric contractions at 30% MVC, increasing to 15 sets of 1 min, 7/wk × 8 wks	Maximal twitch tension	↔ twitch force

1-RM: one-repetition maximum; **MVC:** maximum voluntary contraction; **TMS:** transcranial magnetic stimulation; **wk:** week; **wks:** weeks